IOSR Journal Of Pharmacy www.iosrphr.org
(e)-ISSN: 2250-3013, (p)-ISSN: 2319-4219
Volume 8, Issue 4 Version. III (April 2018), PP. 43-46

High Rates Of Antimicrobial Resistance Of ESBL-Producing *Klebsiella* spp. Causing Bloodstream Infections In Northeast Of Brazil.

Raylane Meneses Marques Dos Santos[1], Wellerson Lucas De Pinho Barreto[1], Cynthia Karolina Rodrigues Do Nascimento[1], Jadiel Silva Reis Filho[1], Victor Brito Dantas Martins[1], Miguel Araújo Rios Neto[1], Vaneska Magalhães Rios[1], Luiza Franco Corá[2], Jacqueline Batista Sousa[2], Kennio Ferreira-Paim[3], Fernanda Machado Fonseca[1*].

[1] *Department of Biomedicine, Federal University of Piaui, Campus Ministro Reis Veloso. São Sebastião Avenue 2819, Reis Veloso, Postal Code: 64204-035, Parnaíba, PI, Brazil.*
[2] *Institute of Biological and Natural Sciences, Federal University of Triangulo Mineiro. Praça Manoel Terra 330, Postal Code: 38015-050, Uberaba, Minas Gerais, Brazil.*
[3] *Department of Infectious and Parasitic Diseases, Triangulo Mineiro Federal University, Frei Paulino Avenue, 130, Postal Code: 38001-170, Uberaba, Minas Gerais, Brazil.*
Corresponding author: Fernanda M. Fonseca.

Abstract: *Klebsiella* spp. can cause various severe human diseases, such as bloodstream infections, pneumonia, and urinary tract infections. Carbapenem antibiotics have been recommended as first-line treatments for the infections that are caused by multidrug-resistant Gram-negative pathogens. However, the emergence and spread of bloodstream infections due to extended spectrum beta-lactamase (ESBL)-producing *K. pneumoniae* has aroused wide public concern all over the world. This cross-sectional and retrospective study aimed to evaluate the antimicrobial susceptibility of ESBL-producing enterobacteria isolated from blood cultures of patients with bloodstream infections in Northeast of Brazil.

Keywords - Klebsiella Infections, Drug Resistance, Microbial, beta-Lactamases.

Date of Submission: 23-04-2018 Date of acceptance: 10-05-2018

I. INTRODUCTION

A significant increase of bloodstream infections caused by extended-spectrum-β-lactamase (ESBL)-producing Enterobacteriaceae in the community have been described. ESBLs are defined as plasmid mediated enzymes produced by some bacterial species and that can hydrolyze most beta-lactam antibiotics [1, 2]. An interesting study about ESBL-producing *Escherichia coli* causing bacteremia have studied 1307 blood culture samples in Sweden, from which *E. coli* was the main ESBL-producing species, detected in 6.1% of cases [3]. In Brazil, the progressive prevalence of ESBL-producing enterobacteria, mainly *Klebsiella pneumoniae*, reaches alarming rates of detection and continues to expand in South America [1]. Recent data showed high rates of resistance monobactams, cephalosporins, fluoroquinolones and sulfonamides of ESBL-producing Enterobacteriaceae isolated from patients with urinary tract infection in Brazil [4, 5]. We provided data from the Northeast of Brazil and evaluated the antimicrobial susceptibility of ESBL-producing enterobacteria isolated from blood cultures of patients during four years at a private laboratory in the city of Parnaiba, PI. It has been detected an increase in antimicrobial resistance to drugs that are commonly used as treatment for bloodstream infections.

II. METHODS

This cross-sectional, retrospective, and epidemiological study was approved by the Research Ethics Committee of Federal University of Piaui (Protocol number 66139617.4.0000.5669). All exams were performed between January 2014 to December 2017. Further information on the samples, such as the age and sex of the patient, isolated microorganism, the result of the antimicrobial susceptibility and disk approximation tests for phenotypic detection of ESBL, were obtained through access to de database of the laboratory. The exclusion criteria included blood culture in which the antibiogram was not performed or the technique of disk approximation was not performed concomitantly. The private laboratory that accepted to participate in the present study signed the consent term, allowing the collection and analysis of data and the test results. The

identity of patients was preserved throughout the time of accomplishment of this study. The data obtained regarding age, sex, isolated microorganisms, susceptibility profile and ESBL-producing were analyzed in SPSS 23.0 software.

III. RESULTS

A total of 115 blood cultures were included. The age of the patients ranged from <1 year of age to 97 years (average age 19.5 ± 28.1 years). Regarding sex, male patients represented 53.9% (n=62) and 46.1% (n=53) were female. All the blood culture presented bacterial growth and all patients have fever or suspicion of sepsis.

Enterobacteriaceae were positive in 89 (77.4%) cases, being *Klebsiella* spp. the most prevalent species detected in 52 (45.2%) blood cultures, followed by *E. coli* detected in 15 (13%) cases. *Staphylococcus* spp. was observed in 14 (12.2%) samples and in 34 (29.8%) blood culture, other species were isolated as the etiological agent.

ESBL-production was demonstrated by the disk approximation technique in 22 (24.7%) out of the 89 enterobacteria isolated, of which 19 (86.4%) corresponded to the *Klebsiella* spp., two (9.1%) were *Enterobacter* spp. and one (4.5%) was *Serratia* spp. The age of patients presenting bacterial growth in blood culture by positive ESBL enterobacteria ranged from <1 year of age to 74 years (average age 8.86 ± 22.98 years).

The antimicrobial susceptibility profiles of ESBL-producing enterobacteria are demonstrated in Table 1. Within carbapenems, susceptibility to imipenem was found in 86.4% (n = 19) and to meropenem in 95.5% (n = 21). Among fluoroquinolone, susceptibility to ciprofloxacin and norfloxacin occurred in 77.3% (n=17) and 22.7% (n=5), respectively.

The ESBL-producing enterobacteria showed resistance in 86.4% (n = 19) to amoxicillin, a penicillin with a beta-lactamase inhibitor, and 81.8% (n = 18) to aztreonam. Resistance was also observed to the first, third and fourth generation cephalosporins in 95.5% (n = 21) to cefotaxime, followed by 90.9% (n = 20) to ceftriaxone, 77.3% (n = 17) to ceftazidime, and 72.6% (n = 16) to cefepime. To sulfonamides (sulfamethoxazole/trimethoprim), 86.4% (n = 19) of the isolates were resistant (TABLE 1).

Table 1: Profile of antimicrobial susceptibility of ESBL-positive enterobacteria (n = 22) and non-ESBL-producing (n=93)

Antibiotic	Antimicrobial susceptibility							
	Sensible N (%)		Resistant N (%)		Intermediate N (%)		Not applicable N (%)	
	ESBL+	Non-ESBL	ESBL+	Non-ESBL	ESBL+	Non-ESBL	ESBL+	Non-ESBL
Amoxicillin	-	28 (30,1)	19 (86,4)	32 (34,4)	-	5 (5,4)	3 (13,6)	28 (30,1)
Ampicillin	-	7 (7,5)	4 (18,2)	31 (33,3)	-	-	18 (81,8)	55 (59,1)
Aztreonam	1 (4,5)	33 (35,5)	18 (81,8)	37 (39,8)	2 (9,1)	-	1 (4,5)	23 (24,7)
Cephalothin	-	2 (2,2)	3 (13,6)	1 (1,1)	-	-	19 (86,4)	90 (96,8)
Cefepime	2 (9,1)	41 (44,1)	16 (72,7)	28 (30,1)	3 (13,6)	2 (2,2)	1 (4,5)	22 (23,7)
Cefotaxime	-	28 (30,1)	21 (95,5)	39 (41,9)	-	1 (1,1)	1 (4,5)	25 (26,9)
Cefoxitin	1 (4,5)	4 (4,3)	1 (4,5)	3 (3,2)	-	-	20 (90,9)	86 (92,5)
Ceftazidime	1 (4,5)	41 (44,1)	17 (77,3)	27 (29)	4 (18,2)	4 (4,3)	-	21 (22,6)
Ceftriaxone	-	30 (32,3)	20 (90,9)	34 (36,6)	-	2 (2,2)	2 (9,1)	27 (29)
Imipenem	19 (86,4)	64 (68,8)	-	6 (6,5)	1 (4,5)	6 (6,5)	2 (9,1)	17 (18,5)
Meropenem	21 (95,5)	65 (69,9)	-	6 (6,5)	-	-	1 (4,5)	22 (23,7)
Ciprofloxacin	17 (77,3)	67 (72)	3 (13,6)	19 (20,4)	1 (4,5)	4 (4,3)	1 (4,5)	3 (3,2)
Levofloxacin	-	15 (16,1)	1 (4,5)	4 (4,3)	-	1 (1,1)	21 (95,5)	73 (78,5)
Norfloxacin	5 (22,7)	15 (16,1)	2 (9,1)	5 (5,4)	1 (4,5)	-	14 (63,6)	73 (78,5)
Amikacin	9 (40,9)	54 (58,1)	13 (59,1)	18 (19,4)	-	5 (5,4)	-	16 (17,2)
Gentamicin	1 (4,5)	38 (40,9)	21 (95,5)	45 (48,4)	-	6 (6,5)	-	4 (4,3)
Sulfamethoxazole / trimethoprim	2 (9,1)	37 (39,8)	19 (86,4)	48 (51,6)	-	2 (2,2)	1 (4,5)	6 (6,5)
Nitrofurantoin	-	5 (5,4)	5 (22,7)	3 (3,2)	1 (4,5)	5 (5,4)	16 (72,7)	80 (86)
Nalidixic Acid	-	-	-	-	-	-	22 (100)	93 (100)

ESBL: Extended-Spectrum Beta-lactamases.

IV. DISCUSSION

A total of 659 samples of enterobacteria isolated from different clinical specimens were evaluated by Abreu et al. [5] in the city of São Luis, Northeast of Brazil, of which 125 (19%) were ESBL-producing, being *K. pneumoniae* the most prevalent species, detected in 50.4% (n=63) cases. In another study, Seki et al. [6]

detected the prevalence of ESBL-producing bacteria in 93 (40.2%) of 231 bloodstream isolates of enterobacteriaceae recovered from patients admitted to general medical wards or intensive care units in Rio de Janeiro, Brazil, being *K. pneumoniae* the most prevalent species. Some studies have suggested that ESBL-positive *K. pneumoniae* bacteremia compared to ESBL-positive *E. coli* bacteremia is often associated with complicated infection and less often with uncomplicated infection such as urinary tract infection [7].

In the present study, the prevalence of ESBL-producing enterobacteria was 24.7% (n=22). *Klebsiella* spp. was the major beta-lactamase producing species, corresponding to 86.4% (n=19). Our data corroborate with those presented by Tuon et al. [8], in the city of Curitiba, Brazil, whose study demonstrated a prevalence of *K. pneumoniae* ESBL-producing in adult patients with bacteremia in 60.6% (n=63) of the 104 cases evaluated, and the rate of mortality reached 49.2%. The detection of ESBL-producing enterobacteria in blood culture is related to higher mortality rates and some studies show that these bacteria are the main cause of septicemia in Brazilian hospitals [1].

Since *K. pneumoniae* is a leading cause of nosocomial infections, the high rates of ESBL production among these microorganisms group is of much concern. Also, the profile of the beta-lactamase producing species may differ both geographically and also in relation to the type of infected patient, it is important to identify and detect the presence of ESBL-producing enterobacteria [9, 10]. In the present study, the resistance rates to gentamicin reached 95.5% for ESBL-producing enterobacteria whereas for non-ESBL-producing bacteria the resistance detected was 48.4%. These results deserve attention, once this high level of resistance to multiple antimicrobials highly limits the treatment options for bloodstream infections in these settings [9]. Another study described a high proportion (82.9%) of invasive bloodstream infections with community acquired ESBL-producing *Klebsiella pneumoniae* in a rural community in Ghana. This high proportion of ESBL-producing *Klebsiella* spp. is worrisome and might be devastating in the absence of second line antibiotics [11].

Some studies have been show an increasing resistance rates to ceftriaxone and an increasing detection of ESBLs worldwide with the highest rates of ESBL production among *Klebsiella* spp. and *E.coli* from Latin America when compared with other regions of the world [12]. This situation may be a consequence of multiple facts such as the indiscriminate use of cephalosporins for common infections as well as the limited infection control measures to reduce the transmission of multidrug-resistant microorganisms. In the present study, the resistance rate to ceftriaxone of ESBL-producing enterobacteria was high (90.9%), while the resistance of non-ESBL-producing bacteria was present in 36.6% of the cases.

V. CONCLUSION

In conclusion, ESBL production was demonstrated in 22 (24.7%) of 89 isolates of Enterobacteriaceae. Of these, 19 (86.4%) were *Klebsiella* spp., two (9.1%) were *Enterobacter* spp., and one (4.5%) was *Serratia* spp. A high susceptibility to carbapanems and quinolones (ciprofloxacin) was observed. However, a high proportion of the isolates showed resistance of beta lactamics, monobactams, cephalosporins, and sulfonamides.

REFERENCES

[1]. S Shaikh, J. Fatima, S. Shakil, et al., Antibiotic resistance and extended spectrum beta-lactamases: Types, epidemiology and treatment. *Saudi J Biol Sci, 22(1),* 2015, 90-101.

[2]. CL Rugini, A.M. Sobottka, and D.B. Fuentefria, Occurrence and sensitivity profile of extended spectrum beta-lactamase-producing Enterobacteriaceae at a tertiary hospital in Southern Brazil. *Rev Soc Bras Med Trop, 48(6),* 2015, 692-698.

[3]. SV Aken, N. Lund, J. Ahl, I. Odenholt, and J. Tham, Risk factors, outcome and impact of empirical antimicrobial treatment in extended spectrum β-lactamase-producing Escherichia coli bacteraemia. *Scand J Infect Dis, 46(11),* 2014, 753-762.

[4]. MA Rios Neto, V.M. Rios, L.F. Corá, M.M. Fonseca, K. Ferreira-Paim, and F.M. Fonseca, High rates of antimicrobial resistance of ESBL-producing Enterobacteriaceae isolated from clinical samples in Northeast of Brazil. *Infect Dis (Lond), 50(3),* 2018, 229-231.

[5]. AG Abreu, S.G. Marques, V. Monteiro-Neto, et al., Nosocomial infection and characterization of extended-spectrum β-lactamases-producing Enterobacteriaceae in Northeast Brazil. *Rev Soc Bras Med Trop, 44(4),* 2011, 441-446.

[6]. LM Seki, P.S. Pereira, M.S. Conceicão, et al., Molecular epidemiology of CTX-M producing Enterobacteriaceae isolated from bloodstream infections in Rio de Janeiro, Brazil: emergence of CTX-M-15. *Braz J Infect Dis, 17(6),* 2013, 640–646.

[7]. C Sakellariou, S. Gürntke, I. Steinmetz, et al., Sepsis Caused by Extended-Spectrum Beta-Lactamase (ESBL)-Positive K. pneumoniae and E. coli: Comparison of Severity of Sepsis, Delay of Anti-Infective Therapy and ESBL Genotype. *PLoS One, 11(7),* 2016, e0158039.

[8]. FF Tuon, M. Kruger, M. Terreri, et al., Klebsiella ESBL bacteremia-mortality and risk factors. *Braz J Infect Dis, 15(6),* 2011, 594-598.
[9]. C García, L. Astocondor, B. Rojo-Bezares, et al., Molecular Characterization of Extended-Spectrum β-Lactamase-Producer Klebsiella pneumoniae Isolates Causing Neonatal Sepsis in Peru. *Am J Trop Med Hyg, 94(2),* 2016, 285–288.
[10]. VQ Dat, H.N. Vu, H. Nguyen The, et al., Bacterial bloodstream infections in a tertiary infectious diseases hospital in Northern Vietnam: aetiology, drug resistance, and treatment outcome. *BMC Infect Dis.* 17, 2017, 493.
[11]. D Eibach, C.B. Campos, R. Krumkamp, et al., Extended spectrum beta-lactamase producing Enterobacteriaceae causing bloodstream infections in rural Ghana, 2007-2012. *Int J Med Microbiol, 306 (4),* 2016, 249-254.
[12]. M Villegas and M. Blanco, Increasing prevalence of extended spectrum-beta lactamase among gram-negative bacilli in Latin America - 2008 update from the study for monitoring antimicrobial resistance trends (SMART). *Braz J Infect Dis, 15(1),* 2011, 34–39.

IOSR Journal of Pharmacy (IOSR-PHR) is UGC approved Journal with Sl. No. 5012

Raylane Meneses Marques Dos Santos "High Rates Of Antimicrobial Resistance Of ESBL-Producing *Klebsiella* spp. Causing Bloodstream Infections In Northeast Of Brazil." IOSR Journal of Pharmacy (IOSRPHR), vol. 8, no. 4, 2018, pp. 43-46